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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,866	02/24/2004	Jia-Ai Zhang	226236	3684

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,866	ZHANG ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-45 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-45 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3-11-04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims included in the prosecution are 1-45.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites, "second liposome forming material" and cholesterol and alpha-tocopherol as Markush members. However, these compounds by themselves do not have the ability to form liposomes.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-6, 8-14, 16-23, 25-33, 39-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rool (6,365,735) in combination Rahman (4,952,408) of record or vice versa.

Rool discloses that vinca alkaloids are known for their anti-cancer activity. According to Rool, Vinorelbine is currently used in the treatment of most widespread from of cancer of lungs and also metastatic cancers of

the breast (col. 2, lines 34-40). Rool lacks the teaching of the liposomal encapsulation of vinorelbine.

Rahman teaches the liposomal encapsulation of vinca alkaloids and their use in combating tumors. According to Rahman, liposomal encapsulation would enable the chemotherapeutic agent to reach its target in a selective and controlled fashion with an enhanced antitumor effect and decreased toxicity (abstract, col. 1, lines 20-68). The liposomes contain cardiolipin, phosphatidylcholine, cholesterol and phosphatidylserine or dicetylphosphate. According to Rahman, a combination of vinca alkaloids can be used. The vinca alkaloid is first complexed with cardiolipin The compositions are lyophilized and contain a sugar such as lactose (col. 2, lines 51-57, col. 3, lines 13-25, col. 4, lines 6-30 and claims). Rahman does not explicitly teach the vinca alkaloid, vinorelbine. Rahman also does not explicitly teach whether the liposomes are unilamellar or multilamellar (MLV) or a mixture. However, since the nature of the liposomes produced depends upon the sonication process (col. 4, lines 12-30), it would be obvious to one of ordinary skill in the art to control the production of both unilamellar and MLV in the composition depending upon the desired goal.

The use of cardiolipin containing liposomes as vehicles for the vinca alkaloid, vinorelbine in the treatment of cancer would have been obvious to one of ordinary skill in the art since Rahman teaches the advantages of these liposomes. Alternately, the use of vinorelbine in the liposomes of Rahman with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since vinorelbine is

art known anti-cancer agent and the reference of Rahman shows the successful use of the liposomes for vinca alkaloids in the treatment of cancer.

5. Claims 15, 21, 33-38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rool (6,365,735) in combination Rahman (4,952,408) or vice versa as set forth above, further in view of Hope (5,800,833).

The teachings of Rool, and Rahman have been discussed above. As pointed out above, Rahman teaches the lyophilization of the composition using the cryoprotectants such as lactose. Rahman however, does not teach the cryoprotectant to be an amino glycoside or sugars such as trehalose and sucrose. Rahman also lacks the inclusion of alpha-tocopherol.

Hope while disclosing anti-neoplastic agent encapsulated liposomes teaches that sugars such as trehalose and sucrose and also amino glycosides (dihydrostreptomycin) protect the lipid vesicles during dehydration. Hope also suggests the inclusion of lipid-protective agents such as alpha-tocopherol to protect the lipids against free radical and lipid peroxidative damages on storage (col. 6, line 35 through col. 7, line 8; col. 9, lines 63-67; col. 11, lines 22-27).

The use of sugars other than lactose or amino glycosides during dehydration of the liposomes taught by Rahman with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since Hope teaches that these compounds also work well during the dehydration step. To include alpha-tocopherol in the liposomes of Rahman would have been obvious to one of ordinary skill in the art

since such an inclusion would protect the lipid vesicles during storage as taught by Hope.

6. Claims 7-8, 10 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rool (6,365,735) in combination Rahman (4,952,408) or vice versa, further in view of Rahman (5,648,090).

The teachings of Rool and Rahman (408) have been discussed above. What are lacking in Rahman are the explicit teachings of the mixture of unilamellar and multilamellar liposomes and also that the charge on the liposomes is positively charged or neutral.

Rahman (090) while disclosing cardiolipin-liposomal (SUVs) formulations containing taxanes teaches that these liposomes overcome the multi-drug resistance in cancer cells. According to Rahman, the liposomes can be either positively charged or negatively charged or neutral and the liposomes can be a mixture of unilamellar and multilamellar vesicles. The cardiolipin liposomes have high encapsulation efficiency (abstract, col. 3, lines 33-46, Example 1, col. 6, line 33 et seq., and claims).

The inclusion of cardiolipin which is also a bilayer forming phospholipid, in the liposomal formulations containing mitoxantrone of Lim would have been obvious to one of ordinary skill in the art since Rahman in 923 and 090 teaches that cardiolipin containing liposomes have higher encapsulation efficiency of anti-cancer drugs such as doxorubicin and taxanes respectively and such liposomes overcome the multi-drug resistance in cancer cells.

The references of Kirpotin (6,110,491), Webb (5,543,152), Sarris (6,723.338) and Janoff (5,922,350) are cited of interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK